

**Remarks:**

Applicant has carefully studied the non-final Examiner's Action. These explanatory remarks are believed to be fully responsive to the Action. The amendments above cancelling claims 1-15 render the rejections raised in the Examiner's Action moot. However, the following remarks are germane to the claims as originally submitted and amended. The amendments to the claims are provided to advance prosecution, as well as more clearly and cleaning define the invention. As set forth below, the amendments were not necessitated by the Examiner's Action. Accordingly, this application is believed to be in condition for allowance.

**The references do not establish a *prima facie* case of obviousness.**

There are three basic criteria to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.<sup>1</sup> Where a *prima facie* case of obviousness is not supported by the facts, as is the case here, the applicant is under no obligation to submit evidence of nonobviousness.<sup>2</sup>

*There is no motivation to combine the references.*

The Office provides the following motivation for combining Yoon with Bowers in support of the rejection for claims 1-3, 7 and 8:

Yoon teaches the detection of a sequence specific to *K. brevis* in the *rbcl* gene using a reverse-transcriptase polymerase chain reaction method, while Bowers describes a real-time polymerase chain reaction using an internal fluorescent probe to detect harmful dinoflagellates in a rapid, homogeneous assay. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with assays based on traditional PCR methodology.<sup>3</sup>

This position is neither supported by facts or law. Yoon does not teach, disclose or describe any unique sequences or a method of detecting them. Yoon, to the contrary, is directed to the goal of

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<sup>1</sup> MPEP §2143

<sup>2</sup> MPEP §2412

<sup>3</sup> Office Action, page 5, lines 9-15

inferring a phylogeny among dinoflagellates, vis-a-vis ubiquitous plastids and the Form I *rbcL* gene, in the context of the broader taxon.<sup>4</sup>

One would not be motivated to combine Bowers with Yoon since Yoon does not teach any method of detecting *K. brevis* in a sample. In Yoon, the identity of all species were known prior to preparation. Pure samples of the known species were then used to determine a phylogeny. Logically, determining the relationship of two species from pure samples of known origin does not amount to a method of detecting the presence of a species in a, logically impure, sample. There can be no motivation to combine two references where the combination would not result in the claimed invention.

*The references do not establish a reasonable expectation  
of success for the proposed combination.*

The prior art can be only be modified or combined to reject claims as *prima facie* obvious if there is a reasonable expectation of success.<sup>5</sup>

The Office asserts that Buck provides evidence of the equivalence of primers.<sup>6</sup> Applicant respectfully points out that none of the references teach a specific primer of which the claimed invention can be an equivalent of. The Office continues, however, placing the following "emphasis" on Buck's findings:

Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1).<sup>7</sup> (emphasis in original)

Applicant respectfully disagrees with the Office's characterization of Buck. The broad interpretation given to Buck by the Office would render all primers obvious. The rejection also disregards the unobvious, and indispensable element, of deciding which sequence to amplify. Just as it is improper to pick and choose elements from the prior art to construct a finding of obviousness, it is improper to pick and choose portions of a particular reference without considering the reference as a whole. An accurate characterization of Buck's findings is clearly outlined in the abstract.

<sup>4</sup> Yoon, page

<sup>5</sup> MPEP §2143.02

<sup>6</sup> Office Action, page 17, lines 10-133.

<sup>7</sup> Office Action, page 17, lines 18-21.

We conclude that under *optimal sequencing conditions* with *highly pure template and primer*, many of the common applied primer designed parameters are dispensable"<sup>8</sup> (emphasis added)

In Buck, a panel of 95 primers were synthesized as controls and 69 primers were submitted as tests. The plasmid template was then *preselected* to contain a test sequence *lacking obstacles to sequence extension* and then *purified* by double banding in CsCl-ethidium bromide isopycnic density gradients.<sup>9</sup> In short, the template was cherry-picked for success; "Therefore, this template was extremely pure and optimal for sequencing." Creating an ideal environment with a template consisting of best-case scenario design can hardly be equated to a real-world environment. Buck clearly states that template purity and technical expertise possibly played greater rolls in the success experienced,<sup>10</sup> rather than the obviousness of the primers. The Office has also disregarded the disclaimer:

Different results may be obtained using less carefully purified DNA templates with unusual sequences or structures in less rigorously controlled sequencing operations.<sup>11</sup>

In short; Buck merely provides evidence of the proposition that when nothing can go wrong, it won't.

*The references do not teach or suggest all the limitations set forth in the claims.*

All claim limitations must be taught or suggested by the prior art to establish *prima facie* obviousness of a claimed invention<sup>12</sup>.

It has been alleged that Yoon "teaches the detection of a sequence specific to *K. brevis* in the *rbcl* gene," as stated above. Moreover, it is the position of the Office that Yoon teaches "a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis*, in a water sample comprising the steps of: identifying a unique gene sequence associated with the organism *K. brevis* (Figure 1A and B and p. 11726, column 1, lines 8-14)."<sup>13</sup> Yoon does not teach any method of detecting the presence of anything in a sample. Also, the passages cited to support these conclusory

<sup>8</sup> Buck, page 528, Abstract

<sup>9</sup> Buck, page 530, column 2. (emphasis added)

<sup>10</sup> *Id.* at page 535.

<sup>11</sup> *Id.* at page 536.

<sup>12</sup> MPEP §2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

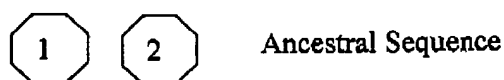
<sup>13</sup> Office Action, page 3, lines 18-19.

statements do not reference any unique sequences. In fact, nothing in Yoon implies that the *rbcl* gene of *K. brevis* has a unique sequence.

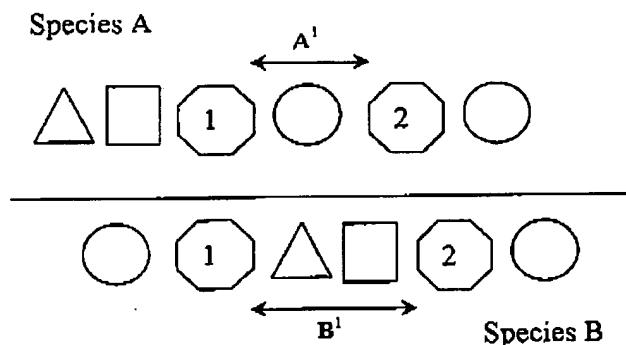
Figures 1A and B of Yoon shows a phylogeny of red algal and red algal-derived plastids using combined *psaA* and *psbA* sequences; both Figures 1A and 1B were created using LogDet values (aka paralinear distances). Distance methods, such as LogDet, attempt to measure the number of changes per site since two species (sequences) split. LogDet analysis provides only distances between sequences but does not reveal sequences, unique or otherwise.

Yoon does not teach, describe or suggest a sequence unique to *K. brevis*. The figures cited merely show that the disclosed genera have varying distances between common sequences of the *psaA* and *psaB* plastids. It cannot be divined from Yoon whether the sequences establishing the paralinear distance in each genera are unique to a species.

Consider the following example wherein sequence 1 and 2 are proximate in a given ancestor.



Varying sequences develop adjacent, and between, the formerly proximate sequences as the ancestor gives rise to diverging species.



Here, the evolution of different sequences between ancestral sequence 1 and 2 yields a variance in paralinear distances ( $A^1$  and  $B^1$ ) sufficient to distinguish Species A from Species B based on LogDet values. The LogDet values, however, represent only the distances between the ancestral sequences and not the sequences themselves. Moreover, although the sequences occur in different loci, no sequence shown in either species is unique.

Continuing with Yoon, page 11726, column 1, lines 8-14:

These data provide strong support, therefore, for the monophyly of fucoxanthin-containing and haptophyte plastids. Our results, using an

expanded data set of *rbcL* sequences, is consistent with previous reports [32]. The two genera of fucoxanthin-containing dinoflagellates, *Karenia* and *Karlodinium*, are paraphyletic at the base of the haptophyte clade, a result that is also found in the *psbA* tree.

The Yoon authors deposited, *inter alia*, *Karenia brevis* *rbcL* gene partial cds in the GenBank Database.<sup>14</sup> The deposit consists of a 907 base long sequence, less than two-thirds of *Karenia*'s *rbcL* gene.<sup>15</sup> The statement that two genera are paraphyletic, *i.e.* composed of some but not all members descending from a common ancestor, has been interpreted as "identifying a unique gene sequence associated with the organism *K. brevis*." Yet Yoon discloses that the Form I *rbcL* gene is the primitive (not derived) condition in dinoflagellates, emphasizing its ubiquitous nature. There is also no teaching of what portion, if any, of the sequence deposited in the GenBank Database is unique to *K. brevis*, or of any method to determine same. Simply stated, the references do not teach or infer that a unique sequence exists.

Yoon infers that LogDet values of *rbcL* and *psbA* sequences can be used to distinguish between genera of dinoflagellates. However, there is no inference or suggestion of any sequence of the *rbcL* gene that is specific to *K. brevis*. Figure 2B shows that several species have identical LogDet values on the species level<sup>16</sup> (species identities were known prior to testing). Bowers does not teach the detection of *K. brevis* sequences; as admitted by the Office.<sup>17</sup>

The Examiner has rejected the specific primers claimed by relying on the "recent" court decision *In re Deuel*<sup>18</sup>. In *Deuel*, as admitted by the Examiner,<sup>19</sup> the Court of Appeals for the Federal Circuit determined the mere existence of a general method of identifying a specific DNA does not make the specific DNA obvious. It is not clear, however, how this case supports the position that the mere existence of a general method of using sequence information for differentiating among taxa would make a primer for a species specific sequence obvious.

The Examiner quotes from *Deuel*, "a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."<sup>20</sup> The following paragraph, which was not provided, states:

<sup>14</sup> Accession No. AY119786

<sup>15</sup> Application, page 3, line 28.

<sup>16</sup> *K. brevis*, *K. mikimotoi*, *Pavlova lutheri* and *Pavlova gyraus* all have Logdet values of 100 on the species level.

<sup>17</sup> Office Action, page 5, line 4.

<sup>18</sup> 34 USPQ2d 1210 (Fed. Cir. 1995)

<sup>19</sup> Office Action, page 16

<sup>20</sup> *Id.*

In all of these cases, however, the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.<sup>21</sup>

The references, alone or in combination, do not disclose a specific, structurally-definable compound. Neither do the references provide any information regarding a sequence unique to *K. brevis*.

Moreover, *Deuel* unambiguously states that a *prima facie* case of unpatentability requires "that the teachings of the prior art suggest *the claimed chemical compounds* to a person of ordinary skill in the art"<sup>22</sup> when new chemical entities are claimed in structural terms (emphasis in original).

A careful reading of *Deuel* makes it clear that while the general idea of claimed molecules, their function, and/or their general chemical nature may be obvious from the prior art, and that the knowledge that some sequence exists, the precise molecules are not obvious without a teaching of the claimed, or closely related, molecule.<sup>23</sup> The Court expressly stated "[a] general motivation to search for some gene that exists does not necessarily make obvious a specifically defined-gene that is subsequently obtained as a result of that search."<sup>24</sup> As was the case in *Deuel*, more is needed and not found here.<sup>25</sup>

#### Examiner's Action

Applicant responds to the outstanding Action by centered headings that correspond to the centered headings employed by the Office, to ensure full response on the merits to each finding of the Office.

#### Claim Rejections – 35 USC §112

Applicant acknowledges the quotation of the second paragraph of 35 USC §112.

Claims 14 and 15 stand rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 14 referred to the unique gene sequence as an 87-base-pair region amplified by RT-PCR, yet in claim 3, the region is a 91-base-pair region. Moreover, claim 15 referred to a unique gene sequence as a 91-base-pair region when amplified by NASBA, yet in claim 10 this region was an 87-base-pair region.

<sup>21</sup> *In re Deuel*, 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995)

<sup>22</sup> *Id.* at 1557

<sup>23</sup> *Id.* at 1558

<sup>24</sup> *Id.*

<sup>25</sup> *Id.*

Applicant thanks the office for pointing out the incongruent claims. Claims 14 and 15 have been cancelled by virtue of the amendments above, rendering the rejection moot. The ambiguity has also been considered in drafting the new claims.

*Claim Rejections – 35 USC §103*

Applicant acknowledges the quotation of the second paragraph of 35 USC §103(a).

Examiner's Action Section 5:

Claims 1-3, 7 and 8 stand rejected under 35 USC 103(a) as being unpatentable over Yoon *et al.* in view of Bowers *et al.* Although the amendments to the claims render the rejection to the specific claims moot, the remarks presented above show that the references cited do not establish a *prima facie* case of obviousness to the claims as originally presented or amended.

While Bowers teaches, generally, a method of detecting the presence of *Pfiesteria* (only) in a sample, the combined references do not disclose a method of detecting the presence of *K. brevis* in a sample by assaying for a species-specific gene sequence. Yoon provides no guidance on detection methods.

Examiner's Action Section 6:

Claims 4-6, and 14 are rejected under 35 USC 103(a) as being unpatentable over Yoon *et al.* in view of Bowers *et al.*, Buck *et al.* and in further view of GenBank Accession No. AY119786. In addition to repeating the grounds of rejection for claims 1-3, 7 and 8, the Office alleges that the purified primer sequence for reverse transcriptase polymerase chain reaction detailed in SEQ. ID. No. 1 is disclosed in the GenBank reference, specifically positions 729-748. As shown below, however, positions 729-748 disclose the exact same sequence as SEQ. ID. No. 1.

GenBank, Accession No. AY119786, 729-748	tgaacgtta ttgggtctgt
SEQ. ID. NO. 1	tgaacgtta ttgggtctgt

Clearly, a primer cannot function where its template is the identical sequence. The rejections for the remaining SEQ. ID. NOs. are similarly flawed.<sup>26</sup> Even assuming the rejection was based on the complimentary sequences to given primers, the GenBank database does not show which

<sup>26</sup> SEQ. ID. No. 2 stands rejected citing positions 819-798 [sic] (neither sequences beginning at 819 or ending in 798 are similar, or complimentary, to SEQ. ID. No. 1); SEQ. ID. No. 3 stands rejected citing positions 758-775, yet these position reveal the identical sequence as SEQ. ID. No. 3 with the exception of the last which is not even complimentary.

of the approximately 2/3 of the *rcbL* gene listed is unique to *K. brevis*. Nothing in the cited references indicates that the *K. brevis rcbL* gene is unique.

The shortcomings of Buck as providing a reasonable expectation of success, and *In re Deuel* providing legal precedent as motivation, are discussed *supra*.

Examiner's Action Section 7:

Claims 9 and 10 stand rejected under 35 USC 103(a) as being unpatentable over Yoon *et al.* in view of Bowers *et al.* and in further view of Leone.

The shortcomings of the cited references have been outlined, *supra*, and nothing in Leone provides a sufficient disclosure to overcome said shortcomings.

Examiner's Action Section 8:

Claims 11-13 and 15 stand rejected under 35 USC 103(a) as being unpatentable over Yoon *et al.*, Bowers *et al.*, Leone *et al.*, Buck *et al.* and in further view of GenBank Accession No. AY119786.

The shortcomings of the cited references have been outlined, *supra*, and nothing in the combination of these five references provides a sufficient disclosure to overcome said shortcomings. The failings of the sequence positions of the GenBank reference are the same here as those discussed in Section 6; no combination of references will make an identical sequence operable as a primer.

**Conclusion**

The Office has not established a *prima facie* case of obviousness. The cited references do not contain all the recited in the claims, as originally presented or as amended; the references do not establish a proper motivation for their combination; and the Examiner has not established a reasonable expectation of success for combining the references. Accordingly all independent claims are presumed to be valid<sup>27</sup> and all claims depending there from are nonobvious as a matter of law.<sup>28</sup>


If the Office is not fully persuaded as to the merits of Applicant's position, a telephone call to the undersigned at (813) 925-8505 is requested.

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<sup>27</sup> MPEP §2142

Very respectfully,  
SMITH & HOPEN

Dated: May 30, 2006  
Reg. No.: 57,422  
Customer No. 21,901

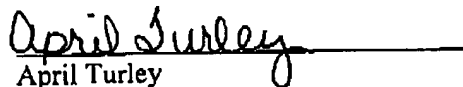
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**CERTIFICATE OF FACSIMILE TRANSMISSION**  
(37 C.F.R. 1.8 (a))

I HEREBY CERTIFY that this Amendment A, including Amendments to the Claims and Remarks, is being transmitted by facsimile to the United States Patent and Trademark Office, Attn: David C. Thomas, Art Unit 1637, (571) 273-8300, on May 30, 2006.

Dated: May 30, 2006

  
April Turley